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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/692,355	10/23/2003	Robert Davies	VPI/00-129-1 DIV US	8543

27916 7590 09/13/2006

VERTEX PHARMACEUTICALS INC.
130 WAVERLY STREET
CAMBRIDGE, MA 02139-4242

EXAMINER	
HABTE, KAHSAY	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 09/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/692,355	DAVIES ET AL.	
	Examiner	Art Unit	
	Kahsay Habte	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/24/2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,17,19-23 and 26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,17,19-23 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-14, 17, 19-23 and 26 are pending in this application.

Response to Amendment

2. Applicant's amendment filed 4/24/2006 in response to the previous Office Action (9/24/2004 and 5/9/2005) is acknowledged. Rejections of claims 1-14, 17-23 and 26 under 35 U.S.C. § 112, first and second paragraph and obviousness-type double patenting rejection (items 2-4, 5a and 5b) have been obviated. Upon further review of the case, it is deemed necessary to raise new issue that needs further rejection.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1-14, 17 and 19-21 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 7,008,948. Although the conflicting claims are not identical, they are not patentably distinct from each other because there is significant overlap between the instant claims 1-14, 17 and 19-21 and claims 1-16 of U.S. Patent No. 7,008,948. Note that the definitions of C, Rx, Ry and R2' and R2 are almost the same (see formula II in claim 1 of the instant claim and formula IV in claim 1 of the U.S. Patent No. 7,008,948).

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-13 and 22-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. It has been recited a method of inhibiting GSK-3 or Aurora activity in a patient and a method of inhibiting the production of hyperphosphorylated Tau protein and phosphorylation of β-catenin in a patient, but the specification is not enabled for such a scope.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed inventions is not single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

Determining if any particular claimed compound would treat any particular claimed disease would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with a number of fundamentally different diseases described below, or to testing them in an assay known to be correlated to

clinical efficacy of such treatment. This is a large quantity of experimentation. The direction concerning treating the claimed diseases is found at pages 2-5 of the specification. Doses required to practice their invention are described at page 28. A 10,000-fold range of doses is recommended. Since no GSK-3 or Aurora-2 inhibitor has ever been used to treat any human disease, how is the skilled physician to know what dose to use for each of these different diseases? There is an in vitro assay, drawn to inhibition of the GSK-3 enzyme, described at pages 333-335 of the specification. There is an in vitro assay, drawn to inhibition of the Aurora-2 enzyme,' described at pages 336-337 of the specification. There is an in vitro assay, drawn to inhibition of the ERK-2 enzyme, described in lines 5-25, page 338. There is an in vitro assay, drawn to inhibition of the Src kinase enzyme, described in the passage spanning lines 22, page 339 to line 31, page 341. Applicants do not assert and it is not art recognized that activity in these four in vitro assays are correlated to clinical efficacy for treating any diseases. There is no working example of treatment of any disease in man or animals. The nature of the invention is clinical treatment of disease with Applicants' kinase enzyme inhibitors, which involves physiological activity. The state of the Tau protein hyperphosphylation pharmaceutical art is summarized by Heutink (Hum Mol Genet.) who states that the relationship between Tau protein and neurodegenerative disease in unclear, first complete paragraph page 984. In the final sentence of the cited paragraph direction for future research is proposed, implying that such inhibitors were not, as of 2000, known to be useful for treating dementia. Fisher (Therapeutic strategies in Alzheimer's disease: M1 muscarinic agonists) states in the first paragraph, column 1,

page 105 that M1 subtype of muscarinic agonists can reduce excess phosphorylation of Tau protein. Yet in the final paragraph on the cited page, he admits that such agonists have failed in clinical trials of Alzheimer's disease.

While compounds working by Applicants proposed mechanism of action might well turn out to be effective for the treatment of AD after additional research, as of 2000, the skilled clinician did not know how to use them for such purposes. The state of the clinical arts in GSK-3 diseases is provided by Eldar-Finkelman (Expert Opinion on Investigational Drugs). Eldar-Finkelman (Expert Opinion on Investigational Drugs) states in the conclusion on page 1516 that diabetes treatment is a possible use of GSK-3 inhibitors.

The artisan using Applicants invention would be a physician with a MD degree and several years of experience, g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The scope of the claims involves all of the thousands of compounds of claim 1 as well as the unknown list of diseases embraced by the terms patients requiring "inhibiting GSK-3 or Aurora activity" and patients requiring "inhibiting the production of hyperphosphorylated Tau protein". Thus, the scope of claims is very broad.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

It is recommended that applicants delete claims 12-13 and 22-23 to overcome this rejection.

6. Claim 26 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of colon, lung, stomach or breast cancer, does not reasonably provide enablement for the treatment of melanoma. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed inventions is not single, simple factual

determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. See for Wands analysis above.

Note that there are four types of melanoma. Three types begin as tumors confined within a site (in-situ tumors), usually within the upper portion of the epidermis. The fourth type is very invasive and quickly penetrates into the lower skin layers and spreads to other areas within the body.

Superficial spreading melanoma (SSM) represents over two-thirds of all cases. An SSM slowly changes over a period of one or several years. It often appears as a dark, flat, or slightly raised mark on the skin with variegated colors. Its borders are irregular and indentations or notches are seen.

Nodular melanoma (NM) represents 15% to 20% of all types of cancer cases. It arises very rapidly, is the most aggressive of all four types of melanoma, and, unfortunately, is also the second most widespread variety. Unlike the superficial spreading variant, which tends to spread outward, the nodular melanoma grows rapidly upward and inward. NM has a typical skin cancer pattern, in that it affects light-skinned individuals' skin that is frequently exposed to the sun, such as the arms, legs, head, and neck (especially the scalp in men).

Acral lentigous melanoma (ALM) is the most common variant of skin cancer that is seen in dark-skinned people. This form of melanoma appears on palms, soles, or on nails. The lesion is usually brown or black, multicolored with irregular borders, and flat

or nodular. This type of melanoma is aggressive and is usually advanced at diagnosis. When present on the nail, it usually involves the thumb or big toe. It may be seen as a black linear band, often with a discolored surrounding cuticle.

Lentigo maligna melanoma (LMM) is the least common variant of melanoma. The nose and cheeks are mostly involved and it is seen in an older population, typically in people in their 70s. The lesions are flat and tan, brown, black, or other colors. The borders can be scalloped and convoluted, and these lesions commonly grow to fairly large sizes (3 cm - 6 cm or larger). Like superficial spreading melanoma, lentigo maligna tends to spread slowly along the surface layers of the skin. Lentigo maligna does not tend to metastasize as some other melanomas do, and, therefore, it is not as threatening.

Since melanoma types are different one from the other, it is impossible to treat these different types with a single pharmaceutical composition. It is recommended that applicants delete "melanoma" to overcome this rejection.

Conclusion

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte whose telephone number is (571) 272-0667. The examiner can normally be reached on M-F (9.00AM- 5:30PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached at (571) 272-0661. The fax phone

number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kahsay Habte
Primary Examiner
Art Unit 1624

September 7, 2006